REMARKS

Claims 1, 4-10, 16-17, 19-20, 23-26, 31-35, 39-41, and 71-72 are currently pending in the above-referenced application. Claims 2-3, 11-15, 18, 21-22, 27-30, 36-38, and 42-70 have been cancelled. Applicant reserves the right to prosecute the subject matter of the cancelled claims in one or more continuation or continuation-in-part applications.

Response To Rejection Under 35 U.S.C. § 103(a)

Claims 1, 4-10, 16, 17, 19, 20, 23-26, 31-35, 39-41, 71, and 72 have been rejected under 35 U.S.C. § 103(a) as unpatentable over Pennanen et al. ("Effect of Liposomal and Free Bisphosphonates on the IL-1β, IL-6, and TNF-α Secretion from RAW 264 Cells In Vitro," *Pharmaceutical Research*, Vol. 12, No. 6, pp. 916-922, 1995) and Hack, et al. (U.S. Patent No. 6,090,777) in view of Yiltalo ("Bisphosphonates and Atherosclerosis," *Gen. Pharmacology*, Vol. 35, pp. 287-296, 2002) and Hope, et al. (U.S. Patent No. 6,139,871). Applicants respectfully disagree with this rejection.

This rejection is premised on a basic misunderstanding of the claim term "having." The Examiner considers the term "having" in the pending claims to indicate that the patient "is in possession of a myocardial infarction, but does not specifically convey that the treatment is *during* the myocardial infarction." Applicants respectfully disagree with this understanding. The dictionary definition of "having" includes "to experience esp[ecially] by submitting to, undergoing, or suffering," for example, having a cold or having a myocardial infarction. (See Merriam-Webster's Collegiate Dictionary, 10th Ed., Merriam-Webster, Inc., Springfield, MA, p. 533 (1997) (submitted herein).) A

skilled person understands that a patient having (or "in possession of") a myocardial infarction would possess the physical characteristics of a patient during an AMI. For example, a patient having an AMI experiences an increase in the number of phagocytic cells in the zone of infarct. (*See, e.g.*, published application at ¶4.) The number of phagocytic cells in the zone of infarct continues to increase in a patient having an AMI for a period of time (*See, e.g.*, published specification at ¶6.) It is this acute activation of phagocytic cells, triggered by the onset of the AMI, that results in the damage at the zone of infarct. (*See, e.g.*, published application at ¶5.) Thus, the physical characteristics of a patient are the same during an AMI as in a patient in possession of an AMI (*i.e.*, having an AMI).

This pending rejection relies on three references that treat chronic diseases, Pennanen, Hope, and Ylitalo. Pennanen treats a "chronic inflammatory disease" while Hope and Ylitalo are directed to treatments for atherosclerosis, which is also a chronic condition. While it may be true that atherosclerosis *can* lead to having an AMI, *preventing* the AMI by treating the atherosclerosis does not equate to *treating* the AMI once it has begun any more than preventing liver failure by treating the underlying alcoholism makes obvious treating the liver failure by transplant once it has already occurred. These chronic treatment method references are then combined with a reference, Hack, that describes the use of a C-1 esterase inhibitor to treat AMI. The Examiner states that this combination of references are applicable to the claimed invention because "none of the instant claims specifically recite emergency treatment of a patient during an acute myocardial infarction." Applicants respectfully disagree.

Applicants have repeatedly evidenced that a patient "having" an AMI, as recited in the pending claims, is in an emergency situation. Everything about "having an acute myocardial infarction" is generally understood to be an urgent, potentially life-threatening condition. The definition of "acute" includes "having a sudden onset, sharp rise, and short course." (*See* Merriam-Webster's Collegiate Dictionary, 10th Ed., Merriam-Webster, Inc., Springfield, MA, p. 12 (1997) (submitted herein).) The skilled person understands that a patient *having* an acute myocardial infarction (as the name plainly indicates) is in a dire condition requiring emergency (*i.e.*, acute) care, quite in contrast to the long-term chronic progression of atherosclerosis, which the Examiner relies on. The skilled person would not look to a treatment for a chronic disease for guidance in finding treatments for acute diseases. Acute diseases require quick and sometimes extreme treatments in contrast with chronic diseases which must be tolerated over long periods of time. Furthermore, as in the alcoholism and liver failure analogy, the site of treatment, or prevention, for the chronic state is different from the site of treatment for the acute one.

A skilled person recognizes that the physical events that occur during an acute disease, such as an AMI, are completely different from those occurring during a chronic disease, such as atherosclerosis. As set forth in the background section of the published application, an AMI prompts a rapid influx of macrophages, which results in tissue injury beyond that caused by ischemia alone. (*See, e.g.*, published application at ¶¶1-8.) The macrophages secrete cytokines which stimulate fibroblast proliferation and promote myocardial damage. It is the acute activation of the macrophages that expand the zone of infarct in a patient having an AMI. (*See, e.g.*, published application at ¶5.)

In contrast, atherosclerosis is a slow-progressive disease which causes a build-up of plaque in the blood vessels. While, over many years atherosclerosis *may* eventually lead to an AMI, once a patient has an AMI it is *far* too late to treat the patient for atherosclerosis. These diseases occur at different times, by different processes, and are mediated by different cells. Thus, a skilled person would not look to treatments for chronic diseases such as atherosclerosis for guidance in identifying treatments for acute diseases such as AMI.

Further, as explained in the response submitted on November 10, 2009, one skilled in the art would not combine Pennanen, Ylitalo or Hope with the Hack reference because, it is understood in the art that liposomes, such as those allegedly described in Pennanen, Hope and Ylitalo, activate the complement system, as evidenced by the article by Szebeni. (*See* Janos Szebeni, "The Interaction of Liposomes with the Complement System," *Critical Reviews in Therapeutic Drug Carrier Systems*, 15(1):57-88 (1998), submitted herein.) However, the Examiner states that the teachings of Szebeni do not apply to this combination of prior art because the liposomes in Szebeni are haptenized and therefore are not the same as the liposomes in Pennanen or the instant claims. (*See* Final Office Action dated February 4, 2010, p. 9.) Applicants respectfully point out that the Examiner has not fully considered the article. The Szebeni article provides a review of the state of the art on liposome-induced activation of the complement system and details studies with both haptenized liposomes and non-haptenized liposomes. In fact, the abstract states that "it has been increasingly recognized that regardless of antigenicity, C activation is an intrinsic property of all charged phospholipid/cholesterol bilayers." (*See*, Szebeni abstract.) The article also

contains a summary of a study by Wassef that shows *non-haptenized* liposomes elicit an antibody-mediated activation of the complement system thereby activating it just as haptenized liposomes. (*See* Szebeni, p. 61.)

Hack describes the use of a C-1 esterase inhibitor to inhibit the complement system as a treatment of acute myocardial infarction (AMI). As evidenced in Szebeni, liposomes (with or without haptens) activate the complement system. Recognizing the incompatibility of these teachings, the skilled person would not combine the teachings of the Hack reference with any of the other cited references which describe the use of liposomes in order to reach the claimed invention. Applicants assert that Hack teaches away from using liposomes to treat AMI because liposomes activate the complement system.

Moreover, one skilled in the art would not be motivated to combine the Hack reference with the other cited references because Hack does not make any suggestion to use a liposome or any other vehicle to deliver the active compound (C1-esterase inhibitor) to the target in order to inhibit the complement system and treat an AMI. Hack clearly states that the target of his treatment is the first component of the complement system. (*See, e.g.*, col. 3, lns. 45-48; col. 4, lns. 6-10; col. 5, lns. 15-18; col. 6, lns. 62-67.) Hack describes that the complement system is inhibited when the C1-esterase inhibitor forms stable complexes with the proteinases that are responsible for activating the first component which are then rapidly cleared from the system. (*See, e.g.*, col. 7, lns. 12-14.) Each molecule of the first component (C1) of the complement system has four esterase sites which the C1-esterase inhibitor binds to. (*See* Markovic, et al., "Acquired C1 Esterase Inhibitor Deficiency," *Ann. Intern. Med.*, 132:144-150, 144

(2000).) Hack teaches away from using a vehicle such as a liposome to deliver the C1-esterase inhibitor because if this inhibitor is encapsulated in a liposome it cannot bind to these esterase sites and form the stable complexes that are required to inhibit the complement system. "If the teachings of a prior-art reference would lead one skilled in the art to make a modification that would render another prior-art device inoperable, such a modification would generally not be obvious." (*In re Gordon*, 733 F.2d 900, 221 U.S.P.Q. 11255, 1127 (Fed. Cir. 1984).) The other cited references provide a teaching or suggestion to use liposomes to deliver the active components which would modify the teachings of Hack and render it inoperable. Thus, one skilled in the art would not combine these cited references and the combination of these references does not render the claimed invention obvious.

Pennanen and Hack may have been combined in the Office Action because they both discuss the inhibition of cytokines to treat inflammatory conditions. (*See* Final Office Action dated February 4, 2010, pp. 3-4.) However, for reasons discussed above one skilled in the art would not combine these references. Claims 19 and 21 of the Hack reference have been specifically pointed out for the teaching of using an agent that is a cytokine antagonist as well as the teaching in Pennanen that bisphosphonates can inhibit cytokine production and secretion. (*See* Final Office Action dated February 4, 2010, p. 4.) Applicants respectfully disagree with the Pennanen-Hack combination. Claims 19 and 21 of the Hack reference recite the administration of a C1-esterase inhibitor in combination with either a cytokine antagonist (claim 19) or a substance having anti-inflammatory properties (claim 21). As discussed in detail above, one skilled in the art would not combine Hack with Pennanen and the other cited references

because placing the C1-esterase inhibitor in a liposome for delivery would render the inhibitor ineffective to inhibit the complement system because it cannot bind to the esterase sites on the first component (C1).

For these reasons, applicants respectfully request that the 35 U.S.C. §103(a) rejection be withdrawn.

Double Patenting Rejection

The pending claims have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of copending Application No. 10/871,488. The claims have also been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4-10, 17-20, 23, 24, 27-29, 32-36, 38 and 41 of copending Application No. 11/190,787. These allegedly conflicting claims are currently undergoing prosecution and have not been allowed, therefore applicants assert that this rejection should be withdrawn and the pending claims of the instant application should be allowed. MPEP 804 states that if "a 'provisional' nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer." Applicants respectfully assert that the above arguments have overcome the pending 103 rejection and thus these two double patenting rejections, based on later filed applications, are the only remaining rejections for this application. Thus, in accordance with MPEP 804, these rejections should be

withdrawn and the pending claims should be allowed. Reconsideration and withdrawal of these rejections are respectfully requested.

CONCLUSION

Based on the foregoing remarks, applicants respectfully request allowance of this application over the Final Office Action of February 4, 2010.

If any issues remain, or if the Examiner has any suggestions for expediting allowance of the application, the Examiner is invited to contact the undersigned attorney.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Pre-Appeal Brief to Deposit Account No. 50-4387, Order No. 92114.005US1.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. 50-4387, Order No. 92114.005US1.

Respectfully submitted,
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Dated: June 30, 2010

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